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(Article begins on next page)

## Reproducibility of Pulmonary Vein Isolation Guided by the Ablation Index: one year outcome of the AIR registry.

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### Conflicts of interest

MA, is consultant for Biosense Webster and has received educational grants from Abbott.

## ABSTRACT

**Aim.** This prospective, multi-center study was designed to evaluate the reproducibility of PV isolation guided by the ablation index (AI).

**Methods.** A total of 490 consecutive patients with paroxysmal (80.4%) and persistent AF underwent first time PV encircling and were divided in four study groups according to operator's preference in choosing the ablation catheter (a contact force (ST) or contact force surround flow (STSF) catheter) and the AI setting (330-450 or 380-500 at posterior and anterior walls, respectively). Radiofrequency energy was delivered targeting interlesion distance  $\leq 6$  mm.

**Results.** At 12 months follow-up a high rate of freedom from AF recurrences was observed in patients with both paroxysmal and persistent AF (91% vs 83.3%,  $p=0.039$ ). There was no difference in the rate of atrial arrhythmias recurrence among the four study groups (4.5% in Group ST330-450, 12.2% in Group ST 380-500, 14.9% in Group STSF330-450, 9.4% in Group STSF380-500,  $p=0.083$ ). Recurrence was also similar between patients treated with a ST (8.0%) or STSF catheter (12.1%,  $p=0.2$ ), within patients targeting an AI settings of 330-450 (10.9%) or 380-500 (10.3%,  $p=0.64$ ), and among operators ( $p=0.84$  and  $p=0.75$  in patients with paroxysmal and persistent AF, respectively).

**Conclusions.** An ablation protocol respecting strict criteria for contiguity and quality lesion resulted in high rate of one-year freedom from AF recurrence, both in patients with paroxysmal and persistent AF, irrespective of the ablation catheters, AI settings, and operator.

**Key words:** atrial fibrillation, catheter ablation, ablation index, reproducibility.

## CONDENSED ABSTRACT

75 In 490 consecutive patients with AF, undergoing first time PV encircling, an ablation  
protocol respecting strict criteria for contiguity and quality lesion resulted in high rate of one-  
year freedom from AF recurrence, both in patients with paroxysmal and persistent AF,  
irrespective of the ablation catheter, AI setting, and operator.

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## What's New

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- This is the first multicenter study to demonstrate the high reproducibility of one-year outcome of AF radiofrequency catheter ablation using an ablation protocol respecting strict criteria for contiguity and quality lesion.

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- The high rate of one-year freedom from AF recurrence was observed both in patients with paroxysmal and persistent AF

- The ablation catheters and the AI settings, chosen by the different operators, did not impact the one-year freedom from AF.

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## INTRODUCTION

160 Catheter ablation is a well-established treatment option for patients with symptomatic atrial fibrillation (AF) and is more successful at maintaining stable sinus rhythm than antiarrhythmic drugs. Pulmonary vein (PV) isolation is the cornerstone of catheter ablation in patients with both paroxysmal and persistent drug-refractory AF. The high rate of arrhythmias recurrence, mainly related to PV reconnection, and the wide outcome variability  
165 among several operators still remain the main limitations of AF catheter ablation (1-3). Recently, several technological improvements have been introduced to improve the efficiency of PV isolation. Among them, the Ablation Index (AI) (Biosense-Webster, Diamond Bar, California), a new marker of radiofrequency lesion quality, allowed a high rate of first pass pulmonary vein (PV) isolation (4-8) and a high single-procedure arrhythmia-free  
170 survival at 1 year (4-7). The aim of this prospective, multi-center study, is to evaluate the reproducibility and outcome of PV isolation guided by the AI.

## METHODS

The Ablation Index Registry (AIR) (ClinicalTrials.gov Identifier: NCT03277976) is a  
175 prospective, multi-center, research study designed to evaluate the acute achievement of PV isolation with ThermoCool SmartTouch (ST) (Biosense-Webster, Diamond Bar, California) or ThermoCool SmartTouch surround flow SF (STSF) (Biosense-Webster, Diamond Bar, California) catheter using the AI Module. Enrollment started in November 2017 and ended in July 2018. The study was approved by local Ethics Committees and complied with the  
180 Declaration of Helsinki guidelines. Written informed consent was obtained from all patients.

**Study population and study protocol.** Enrollment criteria and ablation protocol has been already described (8). Briefly, we enrolled patients with paroxysmal or persistent atrial fibrillation (AF) who underwent their first AF ablation. Each operator performed AF catheter

ablation using its own ablation technique as concerning the ablation catheter (ST or STSF)

185 and the AI setting (380 posterior-500 anterior and 330 posterior-450 anterior). No randomization was required nor was there any deviation from the clinical practice of each center and operator. Therefore the enrolled population was divided in 4 groups: Group ST 330-450, Group ST 380-500, Group STSF 330-450, and Group STSF 380-500.

**Ablation protocol.** The ablation procedure has been already described (8). Briefly, the

190 ablation was usually performed under effective oral anticoagulation, and antiarrhythmic drugs were usually withdrawn before scheduled procedure. Ablation was carried out under conscious sedation or general anesthesia according to operators' preference. One or two transeptal accesses to the left atrium were achieved using a standard approach. Then, a duodecapolar circular mapping LASSO (Biosense-Webster, Diamond Bar, California)

195 catheter and the ablation catheter (ST or STSF) were placed in the left atrium. Left atrium mapping was performed in sinus rhythm. Patients with AF at the beginning of the index procedure underwent electrical cardioversion. After left atrium reconstruction the effective PV-left atrium electrical connection was checked by LASSO catheter. Radiofrequency pulses were delivered using the 3.5-mm Thermocool ST or STSF Catheter in power control mode.

200 Radiofrequency power was set between 20 and 35 W depending on different left atrial sites and the catheter tip was irrigated by saline at a flow rate of 2 mL/min during mapping and of 8 mL/min (STSF) or 17 mL/min (ST) and 15 mL/min (STSF) or 30 mL/min (ST) for outputs of less than and greater than 30 W, respectively (9). Radiofrequency energy was delivered to produce a circumferential ablation around the proximal part of each PV's ostium or around

205 ipsilateral PVs according to the patient's anatomy or operator's preference. The lesion around the PV ostium was created by sequential point-by-point application of radiofrequency energy.

Real-time automated display of RF applications (Carto VISITAG<sup>TM</sup> Module, Biosense Webster) was used with predefined settings of respiration adjustment, catheter stability (3

mm for 3 s), minimum contact force (3 g over minimum 25% of time), with the lesion tag  
210 display size of 3 mm, and AI thresholds: 450 for anterior wall and 330 for posterior wall, or  
500 for anterior wall and 380 for posterior wall. In case of dislocation, a new RF application  
reaching the AI target was applied. Maximal inter tag distance between 2 neighboring Visitag  
was  $\leq 6$  mm (4,10). Upon completion of circumferential ablation a circular mapping LASSO  
catheter was used to confirm PV isolation (first-pass isolation). In the absence of isolation  
215 after completing the circle, LASSO guided touch-up ablation was delivered until PV isolation  
was achieved. Resumption of left atrium to PV conduction was evaluated at 30 minutes after  
ablation. In case of reconnection PVs were newly isolated targeting the points of electrical  
breakthrough.

All patients underwent a post-procedural ECG. Post-procedure echocardiography or other  
220 imaging was at the operators' discretion.

**Post-ablation management and follow-up.** Oral anticoagulation was continued the same  
day of the procedure for all patients and administered for at least 3 months or with no time  
limit in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 2$ . Patients with paroxysmal AF were  
discharged without antiarrhythmic drugs. Patients with persistent AF were discharged with or  
225 without antiarrhythmic drugs according to clinician's preference. Patients were scheduled for  
follow-up examinations 1,3,6, and 12 months after the initial treatment, and the clinical  
assessment of AF recurrence during the follow-up visits was performed by ECG and 24-hour  
Holter monitoring.

Ablation was deemed successful in the absence of symptomatic or asymptomatic atrial  
230 tachyarrhythmias lasting more than 30 seconds identified on surface ECG or on 24-hour  
Holter monitoring, off antiarrhythmic drug therapy. In patients with persistent AF we  
considered the ablation successful in absence of symptomatic or asymptomatic atrial  
tachyarrhythmias regardless of antiarrhythmic drug therapy used. As early relapse of atrial



tachyarrhythmias within the first 3 months after RF ablation may be a transient phenomenon,  
235 this transition period was excluded from the final analysis (11).

**Statistical analysis.** Continuous variables are expressed as mean  $\pm$  standard deviation or median and interquartile range according to their distribution. Normality of data distribution was tested with Shapiro-Wilk test. Categorical variables are expressed as absolute number with percentage (%). Comparison among groups for continuous variables was performed by  
240 the unpaired Student T test or Mann-Whitney U test. Comparison of categorical variables among groups was performed by Chi square test. The rate of freedom from any atrial tachyarrhythmias was assessed by using the Kaplan-Meier curve. Statistical significance was set at a 2-tailed probability level of  $<0.05$ . All statistical analyses were performed using SPSS software (Version 24.0, IBM, Armonk, NY, US).

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## RESULTS

**Study population.** A total of 490 patients were enrolled: 96 patients in ST 330-450 Group, 81 in ST 380-500 Group, 162 in STSF 330-450 Group, and 151 in STSF 380-500 Group. The clinical characteristics of the study population have been already reported (8). Briefly, the  
250 mean age was  $59 \pm 11$  years, 71% of patients were males, the mean body mass index was  $27.1 \pm 4.2$ , the mean left atrium volume was  $104 \pm 49$  ml, the mean left ventricle ejection fraction was  $58 \pm 8$ , 394 (80.4%) patients had paroxysmal AF, 36.8% had hypertension, 6.3% had diabetes mellitus. The left atrium volume was significantly higher in Group ST 380-500, the left ventricle ejection fraction was significantly lower in Group ST 330-450. No other  
255 statistically significant difference was observed among the clinical characteristics of the four study groups.

**Procedural data.** The mean procedural time was  $127 \pm 64$  min, with a mean fluoroscopy time of  $400 \pm 404$  s, and a mean radiofrequency time of  $31.9 \pm 11.8$  min. The rate of first-pass PV

isolation was  $90\pm 16\%$ . Resumption of left atrium to PV conduction 30 minutes after ablation was observed in 5.6% of PVs. The rate of first-pass PV isolation was similar among the four study groups, whereas procedure (ST330  $129\pm 44$  min, ST380  $144\pm 44$  min, STSF330  $120\pm 72$  min, STSF380  $125\pm 73$  min,  $p<0.001$ ) and fluoroscopy time (ST330  $542\pm 285$  s, ST380  $540\pm 416$  s, STSF330  $257\pm 356$  s, STSF380  $379\pm 454$  s,  $p<0.001$ ) significantly differed (8). A complication (4 pericardial effusions, 2 transient phrenic nerve palsy, 1 cardiac tamponade, 1 pneumonia) was observed in 8 (1,6%) patients without any difference among the four study groups ( $p=0.55$ ).

**One year outcome.** One year follow-up was available in 453/490 (92.5%) patients. At 12 months follow-up a high rate of freedom from AF recurrences was observed in patients with both paroxysmal (91%) and persistent (83.3%,  $p=0.039$ ) AF (Figure 1). There was no difference in the rate of atrial arrhythmias recurrence among the four study groups (4.5% in Group ST330-450, 12.2% in Group ST 380-500, 14.9% in Group STSF330-450, 9.4% in Group STSF380-500,  $p=0.083$ ) (Figure 2). At 12 months follow-up the rate of atrial arrhythmias recurrence was also similar between patients treated with a ST (8%) and STSF catheter (12.1%,  $p=0.2$ ) (Figure 3), between patients targeting an AI setting of 330-450 (10.9%) or 380-500 (10.3%,  $p=0.64$ ) (Figure 4), and among operators ( $p=0.84$  and  $p=0.75$ , respectively, in patients with paroxysmal and persistent AF).

## DISCUSSION

The present study demonstrates that an ablation protocol, respecting strict criteria for contiguity and quality lesion, resulted in high rate of one-year freedom from AF recurrence, both in patients with paroxysmal and persistent AF. The results were reproducible among different operators, and were not impacted by the ablation catheters and AI settings chosen.

PV isolation is considered the cornerstone of AF ablation in both paroxysmal and persistent AF. Despite the high acute success rate, achieving durable PV isolation has proven

285 challenging. The high rate (up to 86%) of delayed recovery (12) in PV conduction has translated into disappointing single-procedure success rates (13). Recently a new radiofrequency lesion marker has demonstrated to improve the efficiency of PV isolation. De Pooter et al (14) studied 45 patients undergoing repeat ablation for AF recurrence after first AI guided PV isolation procedure. They found that the likelihood of finding 4 isolated PV at

290 the time of repeat ablation for AF is 62%, higher than previously reported (15), concluding that PV reconnection is no longer the rule in patients with AF recurrence. This finding might justify the favourable acute and 1-year outcome after a PV isolation strategy based on stable, contiguous, and optimized radiofrequency applications by means of AI (4-7). However all these studies were single center and, overall, enrolled 475 patients. In our multicentre study

295 we confirm these findings observing about 90% rate of freedom from AF recurrence. Moreover we reported a high (> 80%) one year success rate also in patients with persistent AF. Our findings were not impacted by the catheter (ST or STSF) chosen nor above all by the AI setting.

There is still a debate on the best AI values that allow effective, safe and durable PV

300 isolation. Das et al (16) studied the relationship between the AI and PV reconnection at repeat electrophysiology study. From receiver operating characteristic (ROC) curve analysis, optimal cutoff points (Youden Index) were calculated. For AI, the optimal cutoff for anterior/roof segments was 376 (sensitivity 63.6%, specificity 77.8%, and positive predictive value 97.2%) and for posterior/inferior segments was 340 (sensitivity 52.9%, specificity

305 94.3%, and positive predictive value 98.2%). No late reconnection was seen in anterior/roof segments where the minimum AI value was  $\geq 480$  or in posterior/inferior segments where the minimum AI value was  $\geq 370$ . El Haddad et al (17) studied acute and late PV reconnection.

By ROC curve analysis they found the highest (90%) specificity to predict durable PV isolation with an AI >550 on the anterior wall and >417 on the posterior wall. We have no data on late PV reconnection, however we did not observe any difference in one year outcome between an AI setting using higher (380-500) or lower (330-450) values. Our findings, might be justified by Ullah et al (15) series. They showed that ablation beyond 430 AI provides minimal additional biophysical efficacy, suggesting an upper limit to use for clinical ablation.

Reproducibility of AF catheter ablation still remains an unsolved issue (1). Radiofrequency ablation, the current most used energy source in most countries (3), of AF is a technically complex procedure, with a long-learning curve, and its results seem to largely depend on Centre's experience. In recent years, cryoballoon ablation of AF has been introduced as an alternative 'single-shot' approach for PV isolation. Several multicenter studies (18,19) showed the higher reproducibility of cryoballoon ablation compared with standard radiofrequency ablation as regards mid-term outcomes of catheter ablation of AF, with lower inter-operator and inter-centre variability. We (8) have already demonstrated that AI guided PV isolation allows comparable rate of acute PV isolation among operator with different skill performing ablation with different catheters, AI settings, procedure and fluoroscopy times. The present study extends this finding on one-year outcome, confirming the high reproducibility of outcome when AF ablation is performed with a point-by-point approach, both in patients with paroxysmal and persistent AF.

**Limitations.** Firstly, this is a non randomized study. No deviation from the clinical practice of each center and operator was required. Nevertheless, AF ablation registries offer a unique opportunity to collect data from large numbers of patients to examine outcomes. In particular, registries might help assess how ablation is being performed in the "real world" compared with controlled clinical trials that are often performed on a highly selected patient

population in very experienced centers. Secondly, a minority of patients (7.5%) were lost to follow-up. This can be explained by the fact that patients were frequently referred for ablation by their local cardiologists and were transferred to their care after discharge. Lastly, sinus rhythm maintenance was based mainly on patients' symptoms, ECG and scheduled 24-hour Holter monitoring. Asymptomatic or short-lasting AF episodes may have occurred unnoticed, and our success rate may have been over-estimated.

## CONCLUSIONS

In conclusion, an ablation protocol respecting strict criteria for contiguity and quality lesion resulted in high rate of one-year freedom from AF recurrence, irrespective of the ablation catheters, and AI settings. The result was reproducible among different operators, both in patients with paroxysmal and persistent AF.

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## FIGURE LEGENDS

**Figure 1. Kaplan–Meier estimation of the time to atrial arrhythmia recurrence after the blanking period in patients with paroxysmal and persistent patients.**

**Figure 2. Kaplan–Meier estimation of the time to atrial arrhythmia recurrence after the blanking period in the four study groups.**

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**Figure 3. Kaplan–Meier estimation of the time to atrial arrhythmia recurrence after the blanking period in patients ablated with the ThermoCool SmartTouch (ST) or ThermoCool SmartTouch SF (STSF) catheter.**

**Figure 4. Kaplan–Meier estimation of the time to atrial arrhythmia recurrence after the blanking period in patients ablated using the high (380-500) or low (330-450) AI setting.**

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